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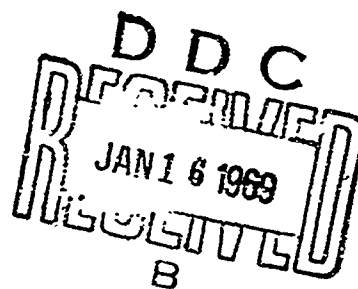
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DEPARTMENT OF THE ARMY
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Title: Infection studies with the virus of milker's node (Infektionversuche mit dem Virus des Melkernotens).

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In regions of cattle breeding, it is a well known fact that the pox-like sickness on the udders of cows can give rise also to infections in persons handling the milk of the cows. Infections in humans lead predominantly to skin alterations on the hands which have been described erroneously in the medical literature by the name "milker's node". In the case of milker's node, one is dealing with rather compact, somewhat hemispherical, swollen, cherry sized nodes which are gray-white to blue-red in color and are usually defined only by a narrow red border since they do not remain completely reactionless with the surrounding skin. The epithelial layer over the node is usually intact but can sometimes be somewhat blistered and raised so that upon spontaneous or artificial breakage, the watery blister contents will appear. Apart from a usually insignificant itchy reaction, the eruptions produce no noteworthy subjective problems. In addition, the general state of health of the patient is, as a rule, disturbed only slightly or not at all. After a pronounced chronic course, the nodes tend to reform gradually after several weeks and then finally disappear completely without leaving behind a scar. In isolated cases, one to two weeks after the appearance of the milker's nodes, a polymorphic eruption also appears - chiefly on the hands and underarms. This usually fades away, however, within a few days. According to the descriptions of most authors, in the case of milker's node, one is dealing histologically with an inflamed granuloma, rich in eosinophilic cells and localized primarily in the upper corium layer. There is also a strong and distinct hyperplastic reaction of the epidermis, however, only relative little degenerative alterations occur there.

Also, in the case of cattle, the infection, which after transmission to humans leads to the development of milker's nodes, as a rule proceeds without any alterations in the general health of the cattle. In agreement with the observation that transmission of the disease is via milk, the skin

alterations of cows are localized primarily on the teats where, depending on the developmental stage of the eruption, nodes, blisters, pustules, or scabs are found. Often, different developmental stages are found simultaneously on the same animal. No particularly painful conditions appear to be associated with the eruptions. As a result, milking of the cow does not usually present any difficulties. Since the food intake of the animals is not noticeably diminished and their milk production scarcely decreased, one usually learns of the udder infections only after the infections associated with the stable personnel have degenerated to the point of being described as milker's nodes.

With regard to the pox-like characteristics of the skin lesions in cattle, these lesions and also the milker's nodes in humans associated with them were believed to ~~was~~ be the result of result of infection with the virus of cow pox*. This opinion is still held by various authors as generally valid for all cases of milker's nodes in spite of the fact that it has been known for a long time that in the majority of cases, the Paul comneal test for the detection of vaccinia virus turns out negative when performed on material from milker's nodes.

On the other hand, other authors have recognized the vaccinal origin of milker's nodes only in those cases where infection by the cow pox virus (vaccinia virus) can actually be proven. In the other cases, an unidentified virus is assumed to be the causative agent. Very probably, however, the vaccinal origin for a relatively small percentage of the milker's node cases reported in the literature can be demonstrated.

* Under the designation "cow Pox", we are considering here any infection of cattle which had been designated by Edward Jenner as cow pox (variola vaccinae, "true" cow pox) and which forms the basis for today's pox vaccination. In this sense, the designation cow pox virus and the synonym, vaccinia virus, have been employed in the following, although according to the investigations of Downie and co-workers, it is known that the vaccinia virus employed today for vaccination has been somewhat modified as compared to the virus of the spontaneously occurring cow pox as the result of numerous passages. The establishment of this fact, therefore, appears to be necessary since the concept "cow pox" has been employed as a designation for milker's node in humans and quite commonly for pustular dermatitis which obviously have nothing to do with genuine cow pox.

First of all, it is a question of those cases in which the Paul corneal test conducted with milker's node material came out positive and typical Guarnier bodies could be detected in the dog cornea (cases of Csontos and Pinter, Kaiser and Weinfurter, Schultze and Grundherr, Schultze, Seifried and Schaaf, Tappeiner) or of cases in which an obvious correlation can be made between the disease in cattle and pox vaccinations occurring in their area in the immediate past (Buchner, Haedo, Hamburger, Jansen, Noordan, Paschen et al.). In addition, milker's nodes, which were used for immunization of experimental animals against subsequent vaccinia infection (for example, in the cases described by Reece and Green), could be considered as vaccinal.

It further noted that genuine cow pox infections (vaccinia infections) of cattle as a rule do not run their course without any reactions in contrast to milker's nodes, but they frequently proceed with considerable injury to the general state of health of the animal. There are fever, exhaustion, loss of appetite, and decline in milk production as can be seen from the descriptions given by Jenner, Hutyrá-Marek, Zuruksoglu, Zwick, and others. Moreover, vaccinia lesions on the udders of cows are usually quite sensitive and the animal, under certain conditions, is difficult to handle (as described previously by Buchner in connection with vaccinal-associated milker's node disease). In addition, lesions on the hands of milkers can occasionally be quite painful - in contrast to the above-mentioned properties of most milker's nodes - and can be accompanied by a more or less significant deterioration of the general state of health. As a result, it can easily be seen that the infection is caused by the virus of true cow pox. According to Kaiser, vaccinia infections on the hands, depending on the predominating conditions, can occur in three forms, namely, first as typical vaccinia lesions, secondly, clinically as paronychia, and thirdly, clinically as milker's nodes. Obviously, the strongly callous nature of the skin on the hands

of milkers is the reason that in these cases, vaccinia virus infection usually takes on the morphological appearance of milker's nodes. However, the fact that typical vaccinia pustules can occur on the hands of milkers after contact with sick cows was shown in the work of Schultze, Seifried, and Schaaf, Buchner, as well as by Oppenheim and Fessler.

As already mentioned, in the majority of cases of milker's nodes, no evidence can be produced for the vaccinal genesis of the disease, that is, no correlation can be made between the disease in cattle and the use of pox protective vaccine in the area; the Paul corneal test comes out negative; the fact that vaccination of animals who have had the disease still results in a typical vaccina lesions thus indicating the absence of vaccina immunity. Nevertheless, many authors still regard milker's nodes as vaccinal qualified in that they represent the view point that the causative agent is an attenuated cow pox (vaccina) virus. Owing to the limited virulence of this agent, in the case of infection of the dog cornea, no typically positive Paul tests are observed. Also, because of the limited immunogenic capability of the virus, the immunity arising from infection can be easily penetrated by reinoculation with the highly virulent virus of the normal pox protective vaccine. This view point has been taken in recent times by Gottron (1930), Gay, Gazorla, and Rodriguez (1935), Frieboes (1936), Petrin (1941), Richter and Kresmann (1950) as well as by Richter and Tat (1954).

If one wishes to share the opinion of these authors, that is, wished to admit that the "milker's node virus" is in reality an attenuated strain of vaccina virus whose immunogenicity is so strongly diminished that the immunity arising from its presence can be easily penetrated by a highly virulent vaccina virus, then one must further logically make the assumption that conversely, in cases of individuals with well developed vaccina immunity, a milker's node

infection could not occur; At present, it has not been demonstrated whether or not "attenuated" vaccina virus is capable of penetrating pre-existing strong vaccina immunity. Our observations in the following work and the investigations with experimental animals show that the milker's node virus is still capable of penetrating the immunity produced by vaccina virus and that this virus could not be an attenuated strain of vaccina virus.

STUDY SERIES I

On 9 September 1953, on a farm in T. (Northern Austria), two cows were purchased from a dealer and added to the eight cows already on the farm. Immediately after purchase, the owner noticed on the udder of one of the new cows a pox-like infection which appeared a few days later on the second cow. Within the course of 8 to 10 days, the infection appeared on all the cows on the farm with the exception of a pregnant cow which had gone dry. The latter cow calved on 22 September, was milked again at this time, and became sick a week later. On 14 October, it was noticed that the mouth of the calf was partly eroded and had scabby lesions on it. The same was true for a second, older calf. The general state of health of the cattle, their appetite, and milk production was not significantly diminished*.

On 16 October, the owner of the farm, who tended the cows together with his wife, noticed an itchy sensation on the thumb and forefinger of his right hand. At these areas there developed within the next few days two typical milker's node lesions with the characteristics described earlier. There was no impairment of the general state of health. The last time the man had been

* For information concerning these cases, we would like to thank J. Kargl, DVH, Trautmannsdorf on the Leitha and also for his assistance.

Immunized against pox was during childhood.

On 16 October, material for research was collected from many of the cows on the farm in T. This was composed of pus envelopes and scabs. The material was stored at -20°C until needed as was all the later virus-containing material that was collected. After the material was collected, all of the cows on the farm were immunized subcutaneously with conventional pox vaccine (glycerine vaccine) on the perineum. By 22 October, all of the cows, in spite of the previous pox-like illness, showed typical vaccine pustules and, it is assumed, had no previous vaccinal immunity.

On 28 November, in an experimental stable in Vienna, a young bull (No. 424) was immunized subcutaneously at many sites on the perineum and scrotum with the scab material from the cows in T. (after grinding the material in physiological saline). Eight days later, there developed at these sites pox-like lesions which showed a certain resemblance to the pox lesions occurring in cattle after vaccination, but exhibited a rapidly occurring and stronger scabbing. On 23 December, approximately four weeks after the first infection, No. 424 was again immunized on the scrotum in the same way as on 28 November with the same material from T. Nine days later, these sites exhibited additional pox-like lesions, which appeared to develop somewhat more weakly than those of the first infection. On 2 January, 1954, the animal was immunized on the perineum with pox vaccine (glycerine vaccine). The lesions which developed by 7 January at this site had the same form as the normal vaccine pustule.

On 23 December, with the material from T., another young bull (No. 425) was also immunized. This animal had been previously employed for the production of pox vaccine (extensive scarification from immunizations on the chest, abdomen, and thighs on 1 December 1953) and must possess accordingly a high degree of

immunity against vaccina virus. The lesions which developed on the animal after infection with the material from T. were identical to those on the non-vaccinated animal No. 424 with regards to development and appearance. Figure 1 shows the scrotum of animal No. 425 with the striated scars from vaccination and the scabby lesions after infection with milker's node virus.

The Paul cornua test was negative not only with the scab material from the cattle in T., but also with the analogous material from animal No. 424 as well with the secretions from the milker's nodes on the hands of the farmer in T.

From the observations in T. and the results of the experimental studies, the following conclusions can be reached: (1) The infectious process induced by milker's node virus is not affected by a previous vaccina infection (see animal No. 425); (2) The infectious process induced by vaccina virus is not affected by a previous infection with milker's node virus (animal No. 424); (3) A previous infection with milker's node virus in the case of cattle results in none or only limited immunity (two cases of infection in animal No. 424).

Figure 1. Scrotum of a young bull infected for five weeks with vaccina virus and 12 days with milker's node virus. a = striated scars after vaccination; b = scabby lesions after infection with milker's node virus. (The reader is referred to the original article for a picture of this figure).

STUDY SERIES II

Originally in December 1958, a farm worker (M.) was admitted to the University Clinic for glandular and skin diseases in Vienna with several typical milker's nodes on his right hand*. The previous history showed that

* On 10 December 1953, the patient was brought to the attention of the Austrian Dermatological Institute by Dr. Santler. For the use of the results of the examination and for the research material from the milker's nodes, we extend our sincerest thanks to Dr. A. Wiedmann, Director of the University Clinic for glandular and skin diseases in Vienna.

Mrs. H. had taken of two cows on a farm in E. (Northerr. Austria), one of which Mrs. H. had previously obtained (on 2 November 1953) from a farm in a neighboring region. Soon after receipt, blisters and pus-forming lesions on the udders were already noticeable on this cow; by the middle of November, the patient had noticed the first signs of milker's nodes for which she went to the Hospital at the beginning of December as already indicated. The Paul corneal test performed with secretions from these milker's nodes gave a negative reaction.

On 11 December 1953, the opportunity was offered to us to examine both the cows in E. In this connection, the new cow which had been obtained six weeks earlier no longer showed udder lesions. On the other hand, the second cow in the stable had pox-like lesions on its udders in various stages of development. This cow had calved on 15 November 1953 and was milked again at this time for the first time. A significant injury to the general state of health of the cow was never observed.

On 11 December 1953, both cows were immunized with vaccina virus. Upon re-examination on 16 December 1953, they showed a typical vaccine pustule at the site of immunization.

3½ months later (on 31 March 1954), the animals were infected subcutaneously with milker's node virus, and also with (a) milker's node secretion from patient H (obtained on 3 December 1953 and stored at 620°C) and (b) with a homogenized scab from animal No. 424, which had been infected with milker's node virus (study series I). Within 9 days, all of the immunizations (in spite of the previous vaccinations) exhibited lesions.

In addition, the milker's node secretions from Patient H were inoculated subcutaneously into the scrotum of a young buff (No. 422) on 23 December 1953. The animal had been previously infected with vaccina virus on 1 December 1953 for the purpose of vaccine production. In spite of the previous immunization against vaccina virus, there developed in this animal lesions at the site of injection which were similar to those seen in non-vaccinated animals. In contrast,

a subsequent immunization with vaccina virus gave no reaction.

From the observations in E. and the results of Study Series II, conclusions similar to those from Study Series I can be drawn: (1) The infection induced by milker's node virus is not affected by a previous vaccina infection (successful infection of both cows in E. as well as animal No. 422 with milker's node virus after a vaccina infection); (2) The infection induced by vaccina virus is not affected by a previous infection with milker's node virus (successful vaccination of both the previously ill cows in E.); (3) The infection with milker's node virus imparted to the cows no or only a short lasting immunity (both of the cows in E. were reinfected successfully with milker's node virus several months after the first infection).

These observations and studies show quite clearly that both the groups of milker's node infections were caused neither by the normal virulent vaccina virus nor by an "attenuated" vaccina virus, but rather by a virus which differs completely from the vaccina virus in antigenic composition. In the case of the causative agent of milker's nodes, if it were a question of an attenuated virus as suggested many times before, then a normal course of infection would not be likely in animals with high vaccina immunity as was the case with both our animals Nos. 422 and 425. Also, the knowledge, that milker's nodes are usually not caused by the virus of cow pox, that is, vaccina virus, leads by necessity to the question as to which other diseases of cattle cause these alterations. The above-mentioned milker's node infection of Patient K. gave us the opportunity to study this question. As already pointed out, this patient had been infected via a cow which had shortly before been obtained from a farm in H. Inspection of the cattle stables in H. had shown that of the approximately 40 cows in this stable, about one-third (see Table 1) showed udder lesions in the form of papular, vesicular, pustular, and scabby lesions. The general state of health of all these animals, which were held for the entire years in a large

fenced-in area, was not impaired in any way. Also, in spite of the udder lesions, the milk production, which was carried out partly by hand and partly by machine, was not decreased to any significant extent. During the second and third inspection of the cattle $3\frac{1}{2}$ and $6\frac{1}{2}$ months later, the percentage of infected cows was approximately the same. The distribution of the disease among the cows, however, had changed as shown in Table 1. Some of the cows showed udder lesions at all three inspections, other at only two of the inspection, while others had lesions had only one of the inspections.

TABLE 1

Results of Three examinations of the cattle stable in H. for pox-like udder lesions.

Animal no.	16 Dec 1953	31 Mar 1954	30 Jun 1954	Animal no.	16 Dec 1953	31 Mar 1954	30 Jun 1954
3	-	-	+	119	+	-	+
8	-	-	-	121	-	-	-
15	-	-	+	125	+	-	+
18	-	-	-	126	-	-	-
23	-	-	-	128	+	?	+
34	-	+	+	129	+	+	-
35	-	+	+	133	-	-	-
37	+	+	+	135	-	-	-
39	+	-	+	136	-	-	-
40	-	-	-	158	-	-	-
41	+	-	-	399	-	-	-
52	-	+	-	400	-	-	-
55	-	+	+	403	-	-	-
68	-	-	-	413	+	-	-
71	+	-	+	416	-	-	-
86	-	+	+	421	-	-	-
104	-	+	-	422	+	+	+
105	-	-	-	426	-	+	-
108	-	-	+	440	-	-	?
111	+	-	-	450	-	-	-
114	+	+	+	1059	-	-	-
118	+	?	+				

Of particular interest are Animals Nos. 71, 119, and 125 which were sick at the first and third inspection but not at the second inspection inbetween.

Hence, it follows that repeated infections at relatively short intervals are possible and that the disease in cattle does not elicit any long lasting immunity. In the veterinary literature, these month and year-long infections in cattle herds have^{been} described as "false pox" (Wirth and Diernhofer) as compared to true cow pox. As is well known, Jenner placed great value on the differentiation of this pox from the actual pox since he knew that the transfer of this disease to man conferred no immunity against small pox. In the veterinary profession, the differentiation between true and false cow pox is of practical importance since cattle stables, upon the appearance of suspicion of true cow pox can be protected by vaccination, as has been shown, for example, by Freger, Krause, Flesky, Csontos, and Pinter, as well as by Meder. In contrast, in other cases where it is a question of false cow pox, the vaccination fails to protect (Hester, Boley, and Graham, Katzenellenbogen).

If one reviews our above-described observations and studies in their totality, and then submits the various opinions expressed in the literature concerning milker's nodes to a critical inspection, then one must come to the conclusion that milker's nodes, generally speaking, are caused by a virus in most, but not necessarily all, cases, which produces so-called "false pox" in cattle (and in various other animals). This virus is so entirely different in antigenic composition from the virus of true cow pox, that is, the vaccina virus, that mutual immunity does not occur in infections with these viruses. In this connection, the investigations of Pantigan and Orth must also be mentioned since they were able to distinguish under the electron microscope distinct morphological differences between vaccina virus and viral elements found in milker's nodes. Further, it should be pointed out that Kaiser (cited by Pantigan and Orth) using the Allergy test of Tieche could not succeed in demonstrating the typical allergen for vaccina virus in milker's node material.

SUMMARY

The pathological alterations, which epidemiologically arise at the hands of milkers under the clinical feature of milker's nodes, can with certainty be traced back to at least two different agents, namely (1) to the virus of true cow pox, which according to Downie and co-workers differs little immunologically from the vaccina virus (the less frequent agent in our area; (2) to a virus which causes relapsing pox-like features known as "false pox" in the veterinary literature (Wirth and Diernhoffer) and which differs considerably from vaccina virus with regards to its antigenic composition. The agent of non-vaccina-induced milker's node is not a weakened cow pox virus since our investigations have shown that animals with high immunity against vaccina still respond to infections with the virus in the same manner as non-vaccinated animals do. () ←

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